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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,462	03/22/2002	Koji Kigawa	084335/0134	4495

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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,462	KIGAWA ET AL.	
	Examin r	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *10-12,15,16 and 18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,13,14 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 March 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *29082001* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I (claims 1-9, 13, 14 and 17) in Paper No. 14102003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 10, 11, 12, 15, 16 and 18-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 14102003.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on August 29, 2001 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-9, 13, 14 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-9, 13, 14 and 17 are indefinite in claim 1. Claim 1 is indefinite over the recitation of "a nonhydrolyzable nucleotide co-factor the number of molecules of which...". It is not clear what is encompassed by the term "the number of molecules of the cofactor". The co-factors listed in the specification and in claim 2 include mixtures of three different compounds, and each of these compounds can potentially have different molar concentrations (= different numbers of molecules), therefore it is not clear which of the compounds are taken into account when calculating the number of molecules. For example, Kowalczykowski et al. (PNAS, vol. 92, pp. 3478-3482, 1995; cited in the IDS), uses ADP/sodium fluoride/aluminum nitrate mixture, with 5mM ADP, 10mM sodium fluoride and 0.4 mM aluminum nitrate (page 3479, third paragraph).

B) Claim 14 recites the limitation "the solid phase" in line 1. There is insufficient antecedent basis for this limitation in the claim. None of the claims from which claim 14 depends (claims, 1, 8 and 13) contain a limitation "a solid phase".

C) Claim 17 recites the limitation "the double-stranded target nucleic acid" in line 1/2. There is insufficient antecedent basis for this limitation in the claim. Claim 1, from which claim 17 depends, does not contain a limitation "a double-stranded target nucleic acid".

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 2, 4-9 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Kigawa et al. (WO 98/08975), as evidenced by Sena et al. (U.S. Patent No. 5,670,316).

Regarding claim 1, Kigawa et al. teach a method of preparing a RecA/single-stranded nucleic acid probe, the method comprising reacting a single-stranded nucleic acid probe sample containing a homologous probe with a RecA-like recombinase in the presence of a nonhydrolyzable nucleotide co-factor the number of molecules of which is one quarter or more of the number of molecules of nucleotide residues in the single-stranded nucleic acid probe and 10 times or less the number of molecules of the RecA-like recombinase (Kigawa et al. teach preparing a RecA-like recombinase/single-stranded DNA complex by mixing a RecA-like recombinase with the homologous nucleic acid probe in the presence of non-hydrolyzable nucleotide cofactor, GTPγS or ATPγS (page 15, lines 4-14; page 14, lines 15-28). Kigawa et al. teach that the reaction mix may contain 0.05-5 mM GTPγS, or 0.01-3 mM ATPγS or 0.3-3 mM ATPγS, 0.002-0.025 mM RecA protein, and 0.5-150 ng of homologous probe per reaction (page 17, lines 2-5). Kigawa et al. do not specifically teach that a number of molecules (= molar concentration) of GTPγS or ATPγS is 10-fold or less than the number of molecules of RecA recombinase, however, if a reaction mix contains 0.05 mM GTPγS and 0.025 mM of RecA recombinase, the number of co-factor molecules is twice the number of RecA molecules. If the reaction mix contains 0.01 mM ATPγS and 0.025 mM of RecA recombinase, the number of co-factor molecules is 0.4 times the number of RecA molecules, etc. Therefore, there are quite a few combinations of reaction conditions under which the number of co-factor molecules is 10-fold or less than the number of molecules of RecA recombinase.

Furthermore, Kigawa et al. teach a specific reaction mixture, No. 23 (Table 1, page 26), which contained 1 ng of 275 bp homologous probe, 500 ng of λ DNA fragments and 15 μg of RecA. The reaction volume was 9 μl, and contained 0.3 mM GTPγS (page 23, lines 7-17). Again,

Kigawa et al. do not specifically teach that a number of molecules (= molar concentration) of GTPγS is 10-fold or less than the number of molecules of RecA recombinase and one quarter (= 25%) or more of the number of molecules of nucleotide residue in the nucleic acid probe. However, calculation of the molar concentrations of RecA and nucleic acid probe gives the following values for the molar concentration of these two components: RecA concentration of 0.044 mM (assuming molecular weight 37,842, as evidenced by Sena et al., col. 2, lines 42, 43), and concentration of the homologous 275 bp probe of 0.011 μM (assuming a molecular weight of one nucleotide of 330). Therefore, the molar ratio of GTPγS to RecA is 6.8, which is less than 10-fold, and the molar ratio of GTPγS to nucleotide residue in the nucleic acid probe is 27,000, which is more than 25% of the number of nucleotide residues in the homologous probe, and Kigawa et al. anticipate limitations of claim 1.)

Regarding claim 2, Kigawa et al. teach ATPγS and ADP. AlF_4 (page 14, lines 15-18).

Regarding claim 4, Kigawa et al. teach a mixture of homologous and heterologous probes (page 8, lines 16-23; page 16, lines 28-31; page 17, lines 1-5; page 23, lines 7-18).

Regarding claim 5, Kigawa et al. teach magnesium ion concentrations from 1-30 mM (page 16, line 31), or 2 mM (page 23, lines 13-18), anticipating the range of 0.5 to 2 mM.

Regarding claims 6 and 7, Kigawa et al. teach RecA from E. coli (page 9, line 14).

Regarding claim 8, Kigawa et al. teach RecA-like recombinase which has a label (page 15, lines 17, 18).

Regarding claim 9, Kigawa et al. teach a homologous probe which has a label or a ligand (page 12, lines 18-23).

Regarding claim 17, Kigawa et al. teach double-stranded target nucleic acid (page 10, lines 3-10).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kigawa et al. (WO 98/08975) and Sena et al. (U.S. Patent No. 5,670,316).

A) Teachings of Kigawa et al. are discussed above. Kigawa et al. do not teach a homologous probe consisting of two at least two types of homologous probes that are sufficiently complementary to one another.

B) Sena et al. teach double-stranded probes for homologous recombination, the probes consisting of two sequences containing regions of complementary overlaps with each other, with a degree of complementarity between 70 and 100% (col. 3, lines 39-44; col. 12, lines 29-46), which is the degree of complementarity considered as substantial by Applicants (page 10, lines 35, 36; page 11, lines 1-10), therefore Sena et al. teach probes with substantially complementary overlap.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the double-stranded probes of Sena et al. in the method of Kigawa et al. The motivation to do so, provided by Kigawa et al., would have been that using double-stranded probes produced probe:target DNA complexes stable to deproteinization (col. 3, lines 25-30).

11. Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kigawa et al. (WO 98/08975) and Kigawa-2 et al. (EP 0 687 738 A1).

A) Regarding claim 13, Kigawa et al. teach RecA-like recombinase labeled with a label or a ligand, but do not teach biotin or digoxigenin. Regarding claim 14, Kigawa et al. teach isolation of

target DNA by capturing a complex of RecA/co-factor/probe labeled with biotin/target DNA with magnetic beads bound to streptavidin (page 17, lines 20-27).

B) Regarding claim 13, Kigawa-2 et al. teach RecA protein labeled with biotin or digoxigenin (col. 10, lines 1-15).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used labeled RecA protein of Kigawa-2 et al. in the method of Kigawa et al. The motivation to do so, provided by Kigawa-2 et al., would have been that labeling the protein provided a sensitive and simple method of detecting hybridization complexes (col. 4, lines 3-11).

12. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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November 12, 2003

JEFFREY FREDMAN
PRIMARY EXAMINER